CHAPTER 8

Breast cancer overview

Risk factors, screening, genetic testing, and prevention

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Breast cancer is the most common malignancy in women, accounting for 32% of all female cancers. Breast cancer also is responsible for 15% of cancer deaths in women, making it the number-two cause of cancer death. An estimated 212,930 new breast cancer cases will be diagnosed in the United States in the year 2005, and 40,410 women will die of this cancer.

This chapter provides an overview of breast cancer, with discussions of epidemiology, etiology and risk factors, genetic cancer risk assessment, signs and symptoms, screening and diagnosis, prevention (including lifestyle changes and chemoprevention), staging, and prognosis. The three chapters to follow focus on the management of stages 0 and I, stage II, and stages III and IV breast cancer.

Epidemiology

Gender Breast cancer is relatively uncommon in men; the female-to-male ratio is approximately 100:1. It accounts for < 1% of all cancer cases in men, and an estimated 460 men will die of the disease in 2005. The incidence of breast cancer in men has remained relatively stable over the past decades, except in Africa, where for unclear reasons, the incidence is rising. *BRCA* mutations are associated with an increased risk for breast cancer in men.

The most common presentation in men is asymmetric gynecomastia, often related to a single effect of drug therapy (such as from digoxin) or liver failure. All palpable masses in men should be carefully examined. Based upon the findings on physical examination, mammography and breast ultrasonography should be considered. Fine-needle aspiration (FNA) or core biopsy can be used to distinguish between gynecomastia and breast cancer. Core biopsy may be performed if the FNA is nondiagnostic.

Age The risk of developing breast cancer increases with age. The disease is uncommon in women younger than 40 years of age; only about 0.8% of breast cancers occur in women < 30 years old and approximately 6.5% develop in women between 30 and 40 years old.

TABLE 1: Survival of women with breast cancer, according to stage, without chemotherapy

Stage	Survival rate at 8 years (%)
I	90
II	70
III	40
IV	10

Race Caucasian women have a higher overall rate of breast cancer than African-American women; however, this difference is not apparent until age 50 and is marked only after menopause. The incidence of breast cancer in American Asian and Hispanic women is approximately half that in American Caucasian women. Breast cancer risk is extremely low in Native-American women.

Geography There is at least a fivefold variation in the incidence of breast cancer among different countries, although this difference appears to be narrowing. The incidence of breast cancer is significantly lower in Japan, Thailand, Nigeria, and India than in Denmark, the Netherlands, New Zealand, Switzerland, the United Kingdom, and the United States. It has been suggested that these trends in breast cancer incidence may be related, in some way, to dietary influences, particularly dietary fat consumption (see section on "Etiology and risk factors").

Socioeconomic status The incidence of breast cancer is higher in women of higher socioeconomic background. This relationship is most likely related to lifestyle differences, such as age at first birth.

Disease site The left breast is involved slightly more frequently than the right, and the most common locations of the disease are the upper outer quadrant and retroareolar region. The risk of contralateral breast cancer in women with *BRCA* mutations is approximately 40% at 10 years after the initial diagnosis of breast cancer. This risk is higher in *BRCA1* than *BRCA2* mutation carriers and those first diagnosed at age < 50.

Risk for breast cancer may be reduced in women who take tamoxifen. It may also be reduced in women who undergo bilateral salpingo-oophorectomy (BSO), especially when this procedure is performed in women younger than age 50. The protective effect of BSO is pronounced among women who develop breast cancer premenopausally.

Survival Survival rates for patients with nonmetastatic breast cancer have improved in recent years (Table 1). These improvements may be secondary to advances in adjuvant chemotherapy and radiation therapy. The contribution of screening mammography to breast cancer-specific survival is variable, favoring a reduction in breast cancer mortality of up to 25% in some series. Its impact on overall survival is less certain.

Etiology and risk factors

Numerous risk factors have been associated with the development of breast cancer, including genetic, environmental, hormonal, and nutritional influences. Despite all of the available data on breast cancer risk factors, 75% of women with this cancer have no risk factors.

Genetic factors Hereditary forms of breast cancer constitute only 5%-7% of breast cancer cases overall. However, the magnitude of the probability that a woman will develop cancer if she inherits a highly penetrant cancer gene mutation justifies the intense interest in predictive testing. Commercial testing is available for several genes (*BRCA1, BRCA2,* and *p53)* that are associated with a high risk for breast cancer development.

Elevated risk for breast cancer is also associated with mutations in the *PTEN* gene in Cowden's syndrome (described later), and a modest increased risk (relative risk of 3.9-6.4) may be seen in women who are heterozygous for a mutation in the *ATM* gene, which is associated with the recessive disease ataxia-telangiectasia in the homozygous state. A moderately increased risk for breast cancer (2-fold for women and 10-fold for men) was recently associated with a variant (1100 delC) in the cell-cycle checkpoint kinase gene, CHEK2, among families without *BRCA* gene mutations.

BRCA1 gene The *BRCA1* gene is located on chromosome 17. This gene is extremely large and complex, and more than 1,000 different mutations have been discovered, distributed along the entire gene. *BRCA1* mutations are inherited in an autosomal-dominant fashion and are associated with an increased risk for breast, ovarian, and, to a lesser degree, prostate cancers. A *BRCA1* mutation carrier has a lifetime risk of developing breast cancer on the order of 56%-85% and a 15%-45% lifetime risk of developing ovarian cancer.

BRCA2 gene The *BRCA2* gene was localized to chromosome 13. *BRCA2* is approximately twice as large as *BRCA1* and similarly complex.

Alterations in *BRCA2* have been associated with an increased incidence of breast cancer in both women (similar to *BRCA1)* and men (6% lifetime risk). Increased risk for ovarian cancer, pancreatic cancer, prostate cancer, and melanoma has also been reported. Together, *BRCA1* and *BRCA2* account for most hereditary breast and ovarian cancer families and approximately half of hereditary breast cancer families.

The incidence of *BRCA* gene mutations in the general breast cancer population is unknown, since most of the data have come from studies of high-risk populations. In one population-based study of women with breast cancer, only 9.4% of women < 35 years of age at the time of diagnosis and 12.0% of women < 45 years old who also had a first-degree relative with breast cancer had germline *BRCA1* or *BRCA2* mutations. However, a 40-year-old woman of Ashkenazi Jewish ancestry who has breast cancer has a 20%-30% probability of bearing one of three founder *BRCA* gene mutations, based on data from high-risk clinics, testing vendors, and Israeli series.

Li-Fraumeni syndrome This rare syndrome is characterized by premenopausal breast cancer in combination with childhood sarcoma, brain tumors, leukemia, and adrenocortical carcinoma. Tumors frequently occur in childhood and early adulthood and often present as multiple primaries in the same individual. Germline mutations in the *p53* gene on chromosome 17p have been documented in persons with this syndrome. Inheritance is autosomal dominant, with a penetrance of at least 50% by age 50.

Cowden's syndrome is inherited as an autosomal-dominant trait and is notable for a distinctive skin lesion (trichilemmoma) and mucocutaneous lesions. Patients with this uncommon syndrome have a high incidence of GI polyps and thyroid disorders; lifetime estimates for breast cancer among women with this syndrome range from 25%-50%. Germline mutations in the *PTEN* gene, located on chromosome 10q23, are responsible for this syndrome.

Family history The overall relative risk of breast cancer in a woman with a positive family history in a first-degree relative (mother, daughter, or sister) is 1.7. Premenopausal onset of the disease in a first-degree relative is associated with a threefold increase in breast cancer risk, whereas postmenopausal diagnosis increases the relative risk by only 1.5. When the first-degree relative has bilateral disease, there is a fivefold increase in risk. The relative risk for a woman whose first-degree relative developed bilateral breast cancer prior to menopause is nearly 9.

Proliferative breast disease The diagnosis of certain conditions after breast biopsy is also associated with an increased risk for the subsequent development of invasive breast cancer. They include moderate or florid ductal hyperplasia and sclerosing adenosis, which pose only a slightly increased risk of breast cancer (1.5-2.0 times); atypical ductal or lobular hyperplasia, which moderately increases risk (4-5 times); and lobular carcinoma in situ (LCIS), which markedly increases risk (8-11 times; see more detailed discussion of LCIS in chapter 9). Patients who have a family history of breast cancer along with a personal history of atypical epithelial hyperplasia have an 8-fold increase in breast cancer risk when compared with patients with a positive family history alone and an 11-fold increase in breast cancer risk when compared with patients who do not have atypical hyperplasia and have a negative family history.

Personal cancer history A personal history of breast cancer is a significant risk factor for the subsequent development of a second, new breast cancer. This risk has been estimated to be as high as 1% per year from the time of diagnosis of an initial sporadic breast cancer. Women with *BRCA*-associated cancer have a 3%–5% per year risk of contralateral breast cancer (cumulative lifetime risk of up to 64% in high-risk cohorts). Women with a history of endometrial, ovarian, or colon cancer also have a higher likelihood of developing breast cancer than those with no history of these malignancies.

Menstrual and reproductive factors Early onset of menarche (< 12 years old) has been associated with a modest increase in breast cancer risk (twofold or less). Women who undergo menopause before age 30 have a twofold reduction in breast cancer risk when compared with women who undergo meno-

pause after age 55. A first full-term pregnancy before age 30 appears to have a protective effect against breast cancer, whereas a late first full-term pregnancy or nulliparity may be associated with a higher risk. There is also a suggestion that lactation protects against breast cancer development.

Radiation exposure An increased rate of breast cancer has been observed in survivors of the atomic bomb explosions in Japan, with a peak latency period of 15-20 years. More recently, it has been noted that patients with Hodgkin's lymphoma who are treated with mantle irradiation, particularly women who are younger than age 20 at the time of radiation therapy, have an increased incidence of breast cancer.

Exogenous hormone use Epidemiologic data provide strong evidence for an association between plasma estrogens and breast cancer risk.

The 1996, large meta-analysis of the relationship between oral contraceptive use and breast cancer risk showed that a history of recent oral contraceptive use, rather than duration of use, was a better predictor of breast cancer risk. (Meta-analysis consisted of 54 earlier studies including 53,297 women with breast cancer and 100,239 women without breast cancer.) The increase in risk for current users was modest (24% for ever users vs never users). These data were based primarily on older high-dose and moderate-dose oral contraceptive pills and not the recently introduced low-dose pills. It is, therefore, likely that the small increase in breast cancer risk associated with the early formulations of oral contraceptives will diminish with the new low-dose pills.

In regard to hormone replacement therapy (HRT) or postmenopausal hormone use results from the Women's Health Initiative (WHI) showed that the overall risks of estrogen plus progestin outweigh the benefits. This large randomized clinical trial sponsored by the National Institutes of Health (NIH) included more than 16,000 healthy women. Results from the WHI trial were published in 2002 after an average 5.6 years of follow-up and included a 26% increase in risk of invasive breast cancer among women taking estrogen plus progestin, compared with women taking placebo. In addition, in women taking these hormones, there were increased risks of heart disease, stroke, and blood clots.

The NIH stopped the estrogen-alone arm of the WHI trial in March 2004. No increase in breast cancer risk was observed in the estrogen-alone arm during the study period (7 years of follow-up). The NIH concluded that estrogen alone does not appear to increase or decrease a woman's risk of heart disease, although it does appear to increase her risk of stroke and decrease her risk of hip fracture.

Alcohol Moderate alcohol intake (two or more drinks per day) appears to modestly increase breast cancer risk.

High-fat diet Diets that are high in fat have been associated with an increased risk for breast cancer. Women who have diets high in animal fat from red meat or high-fat dairy foods have an increased risk of developing breast cancer. Whether the increase in breast cancer risk is associated with the fat content or an unknown carcinogen in these foods is unclear.

TABLE 2: Features indicating an increased likelihood of a *BRCA* mutation

Multiple cases of early-onset breast cancer
Ovarian cancer (with a family history of breast or ovarian cancer)
Breast and ovarian cancer in the same woman
Bilateral breast cancer
Ashkenazi Jewish heritage
Male breast cancer

Obesity Alterations in endogenous estrogen levels secondary to obesity may enhance breast cancer risk. Obesity appears to be a factor primarily in postmenopausal women.

Genetic cancer risk assessment

Genetic testing clearly has the potential to benefit carefully selected and counseled families. Education and adequately trained health care professionals are key elements in the successful integration of genetic cancer risk assessment into clinical practice.

The genetic risk assessment process begins with an assessment of perceived risk and the impact of cancer on the patient and family. This information forms the framework for counseling.

Comprehensive personal and family histories Detailed information regarding personal, reproductive, and hormonal risk factors is noted. Family history, including age at disease onset, types of cancer, and current age or age at death, is obtained for all family members going back at least three generations.

Documentation of cancer cases is crucial to accurate risk estimation. Pathology reports, medical record notes, and death certificates may all be used in determining the exact diagnosis.

Pedigree construction and evaluation The family pedigree is then constructed and analyzed to determine whether a pattern of cancer in the family is consistent with genetic disease. Sometimes, small family structure or lack of information about the family limits assessment of a hereditary trait; other times, clues, such as ancestry or early age at diagnosis, influence risk assessment and the usefulness of genetic testing.

Individual risk assessment Several models are used to estimate the likelihood that a detectable *BRCA1* or *BRCA2* mutation is responsible for the disease in the family. The BRCAPRO computer program is a cancer risk assessment tool that uses a family history of breast or ovarian cancer in first- and second-degree relatives to calculate the probabilities that either a *BRCA1* or

TABLE 3: Risk management options for *BRCA* mutation carriers[a]

Recommended for breast cancer detection
Monthly self-examination of the breast beginning in late teen years
Beginning at age 25 (or at least 10 years before the earliest onset cancer in the kindred):
Clinician breast examination every 6 months
Annual mammography
Consider breast MRI every 1-3 years if there is significant mammographic density
Discussed as options:
Bilateral risk reduction mastectomy (total or skin-sparing)
Participation in clinical trials for chemoprevention (ie, STAR)
Recommended for ovarian cancer detection or prevention
Pelvic examination and PAP smear annually
Serum CA-125 every 6-12 months
Transvaginal ultrasonography every 6-12 months
Discussed as options:
Risk reduction salpingo-oophorectomy upon completion of childbearing
Reproductive counseling (? earlier childbearing)

[a] Also offered to women at increased risk because of a positive family history of hereditary breast and ovarian cancers but for whom genotypic information is not available.

BRCA2 mutation is responsible for the disease. It includes a Bayesian calculation to account for age-specific penetrance differences. If genetic testing is not performed or results are uninformative, the empiric breast cancer risk is estimated by the phenotype as well as the Claus model (derived from the Cancer and Hormone Study, which uses age at onset of breast cancer among first- and second-degree relatives). Personal and family characteristics that are associated with an increased likelihood of a *BRCA1* or *BRCA2* mutation are summarized in Table 2.

Education about the principles of genetics and hereditary cancer patterns is provided. Information on the application of genetic testing (appropriateness, limitations, advantages, and disadvantages) is also given.

Genetic counseling and testing Informed consent is obtained before genetic testing is performed. For individuals who decide to undergo testing, a post-test counseling session is scheduled to disclose and explain the results in person.

Customized screening and prevention recommendations Regardless of whether or not a woman undergoes genetic testing, a customized management plan is delineated, with the goal of prevention or early detection of malignancy, within the context of her personal preferences and degree of risk (Table 3).

Laboratory methods

Several techniques/strategies for detecting mutations in cancer genes have been adopted by different researchers and commercial vendors. Current technology misses 8%-10% of pathologic alterations in *BRCA1* and *BRCA2* (generally large rearrangements).

Directed assays are available for specific founder or ancestral mutations that are common in a given population. Among Ashkenazi Jews, 1 in 40 individuals bears one of three founder mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2)*; these mutations account for 25% of early-onset breast cancer in this population. Moreover, 95% of Ashkenazi Jews with a *BRCA* gene mutation will have one of the three founder mutations.

The lifetime risk of breast cancer was 82% among founder mutation carriers in a large cohort of Jewish families identified via a New York breast cancer study. The lifetime risk of ovarian cancer was 54% for *BRCA1* and 23% for *BRCA2*, similar to the risk in multiplex families from the Breast Cancer Linkage Consortium. However, a population-based study indicated a lifetime breast cancer risk of 40%-73%.

Limitations All of the approaches to detecting mutations have limitations. In general, discovery of an inactivating or "deleterious" mutation of either *BRCA1* or *BRCA2* indicates a high probability that a person will develop breast and/or ovarian cancer.

One of the greatest challenges is the interpretation of missense mutations. These mutations are more likely to be significant if located in an evolutionarily conserved or functionally critical region of the protein. In the absence of a clear disease association, it is often difficult to exclude the possibility that a given missense alteration simply represents a rare polymorphism. A testing service may designate such changes as "genetic variants of uncertain significance."

Testing strategies

In general, testing should be initiated with the youngest affected individual in a given family. Even if one is convinced that a family has hereditary breast and ovarian cancers based on clinical criteria, there is only a 50% chance that an offspring or sibling of an affected patient will have inherited the deleterious allele. Therefore, only a positive test result (detection of a known or likely deleterious mutation) is truly informative.

Until the "familial mutation" is known, a negative test result could mean either that the unaffected person being tested did not inherit the cancer susceptibility mutation or that the person inherited the disease-associated gene but the mutation was not detectable by the methods used.

In many cases, no affected family members are available for testing. In that case, one may proceed with genetic testing of an unaffected person, but only after she has been thoroughly counseled regarding its risks, benefits, and limitations.

Unless there is a suggestive family history, cancer susceptibility testing is not considered appropriate for screening unaffected individuals in the general popu-

lation. However, it may be reasonable to test unaffected persons who are members of an ethnic group in which specific ancestral mutations are prevalent and whose family structure is limited (ie, the family is small, with few female relatives or no information due to premature death from noncancerous causes).

A recent study of 491 women with stage I or II breast cancer and a known familiar *BRCA* mutation indicated that the risk of contralateral breast cancer is approximately 40% at 10 years and is reduced in women who take tamoxifen or who undergo premenopausal oophorectomy *(Metcalfe K, Lynch HT, Ghadirian P, et al: J Clin Oncol 22:2328-2335, 2004).*

Impact of genetic cancer risk status on management

Data from the Breast Cancer Linkage Consortium (BCLC) suggest that the cumulative risk of developing a second primary breast cancer is approximately 65% by age 70 among *BRCA* gene mutation carriers who have already had breast cancer. Thus, knowledge of the genetic status of a woman affected with breast cancer might influence the initial surgical approach (eg, bilateral mastectomy might be recommended for a mutation carrier instead of a more conservative procedure). Moreover, since ovarian cancer risk may be markedly increased in women with *BRCA1* mutations (and to a lesser degree with *BRCA2* mutations), additional measures, such as surveillance for presymptomatic detection of early-stage tumors or consideration of oophorectomy, may be warranted. According to data from *BRCA* carriers who underwent risk reduction salpingo-oophorectomy (RRSO), breast cancer risk may also be decreased by the reduction in ovarian hormone exposure.

Retrospective data suggest that bilateral mastectomy in women who are at high risk for the disease based upon family history significantly reduces the risk for developing breast cancer by approximately 90%. Women who opt for risk reduction mastectomy should be offered reconstruction. Skin-sparing mastectomy may enhance the cosmetic results of reconstruction and should be discussed with the patients' surgeon. This procedure entails removing the breast tissue (including the nipple-areolar complex).

Potential benefits and risks of genetic testing

The ability to identify individuals at highest risk for cancer holds the promise of improved prevention and early detection of cancers. Patients who are *not* at high risk can be spared anxiety and the need for increased surveillance. Recent studies suggest a better emotional state among at-risk relatives who undergo testing than among those who choose not to know their status. The patient's perception of risk is often much higher than risk estimated by current models.

The efficacy of bilateral risk reduction mastectomy (RRM) was recently confirmed in a large prospective study of 483 women with *BRCA* mutations. With a mean follow-up of 6.4 years, RRM reduced the risk of breast cancer by 90% (95% in women who also underwent risk reduction salpingo-oophorectomy; *Rebbeck TR, Friebel T, Lynch HT, et al: J Clin Oncol 22:1055-1062, 2004*).

Potential risks Potential medical, psychological, and socioeconomic risks must be addressed in the context of obtaining informed consent for genetic testing.

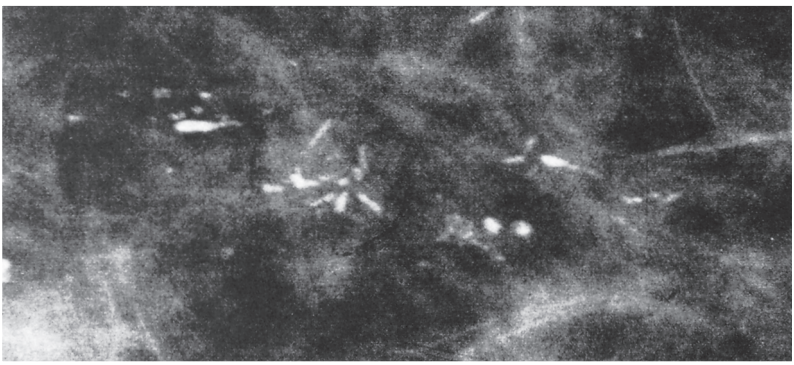

FIGURE 1: Malignant calcifications (comedocarcinoma) in a classic linear dot and dash configuration (BI-RAD 5 lesion). BI-RAD = Breast Imaging Reporting Data System.

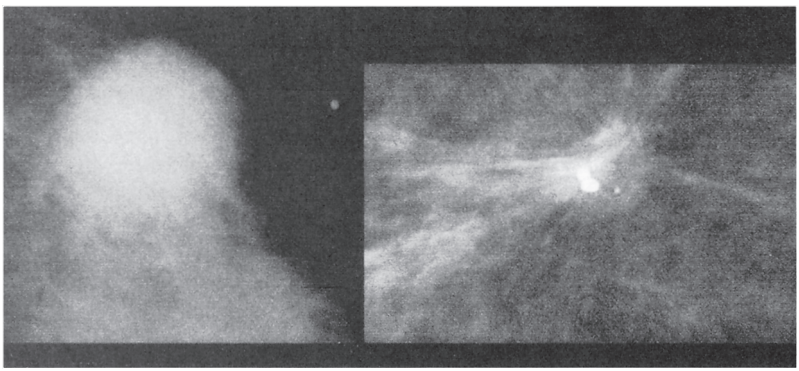

FIGURE 2: Left panel: A dense mass with partially unsharp margins (BI-RAD 4 lesion), which proved to be a fibroadenoma. Right panel: A small, spiculated mass (BI-RAD 5 lesion), which has engulfed a coarse, benign calcification. This lesion proved to be an invasive ductal carcinoma, not otherwise specified (NOS). BI-RAD = Breast Imaging Reporting Data System.

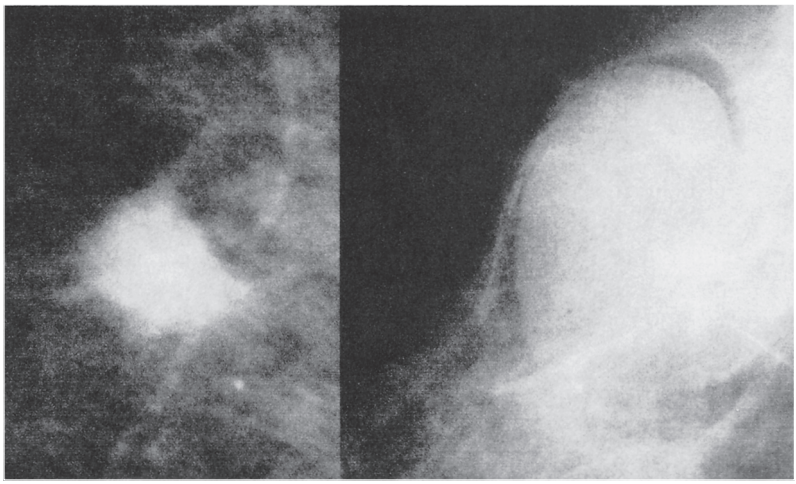

FIGURE 3: Left panel: This focal mass with truly nonsharp margins (BI-RAD 4 lesion) was diagnosed as a tubular carcinoma on stereotactic core biopsy. Right panel: A well-circumscribed lesion containing fat (BI-RAD 2 lesion), which is pathognomonic for a breast hamartoma (fibroadenolipoma). BI-RAD = Breast Imaging Reporting Data System.

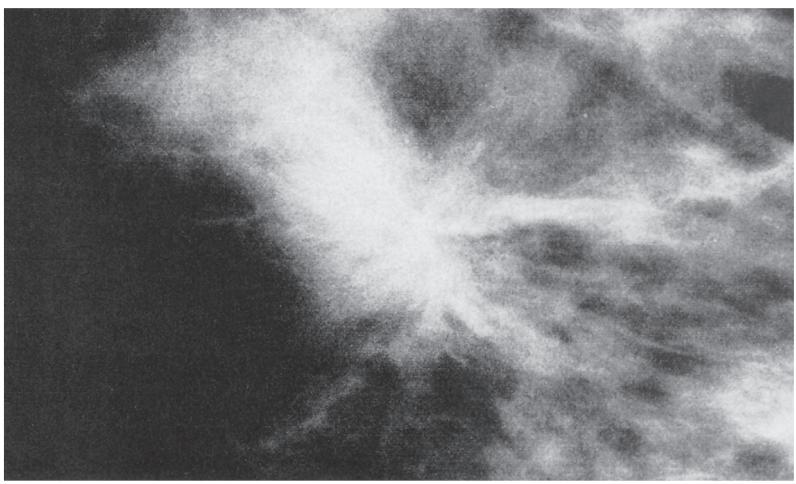

FIGURE 4: Focal architectural distortion may be difficult to see, but, if confirmed, it has the highest positive predictive value for breast carcinoma. This BI-RAD 4 lesion proved to be an invasive lobular carcinoma, which often has a subtle mammographic appearance. BI-RAD = Breast Imaging Reporting Data System.

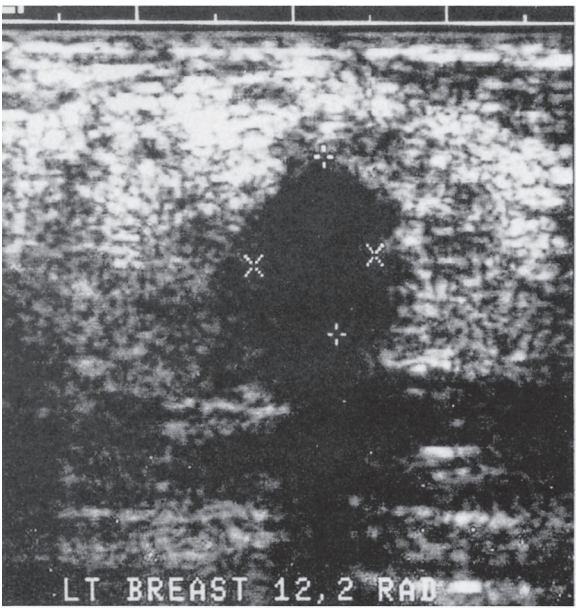

FIGURE 5: This breast ultrasonographic image demonstrates a hypoechoic, solid mass, which exhibits posterior shadowing and is taller than wide. This BI-RAD 4 lesion proved to be an invasive ductal carcinoma, not otherwise specified (NOS). BI-RAD = Breast Imaging Reporting Data System.

Concerns about insurance Fear about adverse effects of testing on insurability remains the premier concern among patients. Close behind that is concern about the costs of analyzing large complex genes ($2,975 for full sequencing of *BRCA1* and *BRCA2).*

Legal and privacy issues The legal and privacy issues surrounding genetic testing are as complex as the testing technologies. Although several state laws regarding the privacy of medical information, genetic testing, and insurance and employment discrimination have been passed, they vary widely.

The 1996 Health Insurance Portability and Accountability Act (US public law 104-191) stipulates that genetic information may not be treated as a preexisting condition in the absence of a diagnosis of the condition related to such information. It further prohibits group medical plans from basing rules for eligibility or costs for coverage on genetic information. However, the law does not address genetic privacy issues and does not cover individual policies. Many states have laws addressing genetic discrimination, but gaps remain.

FIGURE 6: A 42-year-old woman presents with axillary adenopathy, which was positive on fine-needle aspiration. Results of a clinical breast exam, mammography, and ultrasonography were normal. A 7-mm enhancing cancer is clearly seen on this MRI of the breast.

TABLE 4: BI-RAD classification of mammographic lesions

BI-RAD class	Description	Probability of malignancy (%)	Follow-up
0	Needs additional evaluation	1	Diagnostic mammogram, ultrasonographic image
1	Normal mammogram	0	Yearly screening
2	Benign lesion	0	Yearly screening
3	Probably benign lesion	< 2	Short interval follow-up
4*	Suspicious for malignancy	20	Biopsy
5	Highly suspicious for malignancy	90	Biopsy
6	Biopsy-proven malignancy	100	Treatment

BI-RAD = Breast Imaging Reporting Data System

* As an internal option, the ACR recommends that each site be divided into three subcategories: 4A, low suspicion; 4B, intermediate suspicion; and 4C, moderate concern but not classic for malignancy.

ASCO recommendations for genetic testing

Updated guidelines from the American Society of Clinical Oncology (ASCO) recommend that cancer predisposition testing be offered only in the following situations: (1) a person has a strong family history of cancer or early onset of disease; (2) the test can be adequately interpreted; and (3) the results will influence the medical management of the patient or family member. The National Comprehensive Cancer Network (NCCN) published practice guidelines for genetics/familial high-risk cancer screening, and up-to-date versions are available at www.nccn.org.

Signs and symptoms

Mammographic findings Increasing numbers of breast malignancies are being discovered in asymptomatic patients through the use of screening mammography. Mammographic features suggestive of malignancy include asymmetry, microcalcifications, a mass, or an architectural distortion.

When these features are identified on a screening mammogram (see Figures 1-5), they should, in most cases, be further evaluated with a diagnostic mammogram (and, in some cases, with a breast ultrasonographic image or in highly selected cases, MRI [Figure 6]) prior to determining the need for a tissue diagnosis. Often, pseudolesions, such as those caused by summation artifact, dust on the mammographic cassettes, and dermal calcifications, are correctly identified in this manner. All mammographic lesions (and the examinations themselves) must be unambiguously categorized according to one of the six Breast Imaging

Reporting Data System (BI-RAD) classifications developed by the American College of Radiology (ACR, Table 4).

Breast lump When signs or symptoms are present, the most common presenting complaint is a lump within the breast. The incidence of this complaint can range from 65%-76%, depending on the study. Inflammatory breast cancer is particularly aggressive, although relatively uncommon, accounting for about 5% of all breast cancers. On breast palpation, there often is no definite mass, but the breast appears to be engorged with erythema, skin edema (peau d'orange), and skin ridging. Ultrasonography may help to distinguish mastitis or abscess from inflammatory breast cancer. Antibiotics, which are prescribed for presumed mastitis, are not helpful for women with inflammatory carcinoma.

Paget's disease has been associated with intraductal carcinoma involving the terminal ducts of the breasts and may have an associated invasive component. It presents as an eczematoid change in the nipple, a breast mass, or bloody nipple discharge. Cytology may be helpful in establishing the diagnosis; however, negative cytologic results should not preclude a biopsy.

Other local symptoms Breast pain is the presenting symptom in ~5% of patients, breast enlargement in 1%, skin or nipple retraction in ~5%, nipple discharge in ~2%, and nipple crusting or erosion in 1%.

Screening and diagnosis

Screening

Breast self-examination The role of breast self-examination is controversial. The American Cancer Society (ACS) recommends that, beginning in their 20s, women should be instructed in the technique and informed about both the benefits and limitations of this screening tool. Other groups have suggested that routine breast self-examination may lead to more false-positive results and therefore more benign biopsies. One meta-analysis of 12 studies involving a total of 8,118 patients with breast cancer correlated the performance of breast self-examination with tumor size and regional lymph node status. Women who performed breast self-examination were more likely to have smaller tumors and less likely to have axillary node metastases than those who did not.

A major problem with breast self-examination as a screening technique is that it is rarely performed well. Only 2%-3% of women do an ideal examination a year after instruction has been provided.

Clinical breast examination The ACS recommends that women begin clinical breast examination at the age of 20 and have an examination every 3 years between ages 20 and 39, and annually beginning at age 40. Beginning at age 40, the clinical breast examination should be timed to occur near or prior to screening mammography. If the clinician detects an abnormality, the patient should then undergo diagnostic imaging rather than screening. Clinical breast examination should be performed and a complete breast history obtained when a woman presents for routine health care. The clinical examination should include inspection and palpation of the breast and regional lymph nodes. Be-

Breast imagers and surgeons are increasingly utilizing breast MRI. Bedrosian et al reported that preoperative breast MRI changed the planned surgical approach in 26% of cases, including 16.5% of cases of breast conservation switched to mastectomy. Breast MRI has a high sensitivity, and recent technical and clinical developments have improved its specificity. For example, a dedicated breast MRI workstation that performs parametric mapping of dynamic IV contrast enhancement across the whole breast volume is available. It allows the reregistration of subtracted images to reduce motion noise. The indications for breast MRI include searching for an occult primary tumor in the setting of a known positive metastasis, evaluating a borderline lesion of a lesion obscured by dense tissue, and assessing lesions in implant-augmented breasts. Ongoing clinical trials are being performed on screening breast MRI for high-risk women, such as in *BRCA1* and *BRCA2* carriers. At a number of leading breast cancer centers, almost all the women undergoing breast cancer treatment now undergo a breast MRI at some point *(Bedrosian I, Mick R, Orel SG, et al: Cancer 98:468-473, 2003)*.

tween 14% and 21% of breast cancers are detected by clinical breast examination.

Mammography Despite conflicting coverage in the lay press, the benefit of screening mammography is well established by the findings of an evidence-based clinical trial (see Jackson reference). The ACS, the ACR, and the American Medical Association have updated their guidelines since 1997 and recommend annual mammography beginning at age 40. The National Cancer Institute (NCI) also updated its guidelines in 1997, recommending that women undergo screening mammography every 1-2 years beginning in their 40s. The US Preventive Services Task Force updated its guidelines in 2002 and now recommends mammography every 1-2 years, alone or with clinical breast examination, for women aged 40 and older.

Screening mammography is performed in the asymptomatic patient to detect an occult breast cancer. This contrasts with diagnostic mammography, which is performed in a patient with a breast abnormality (palpable mass, bloody nipple discharge, or some other clinical finding) to further identify the etiology of the problem.

Physical examination and mammography are complementary. Mammography has a sensitivity of 85%-90% and, thus, would miss 10%-15% of clinically evident tumors while detecting the majority of cases an average of 2 years prior to any perceptible clinical signs or symptoms.

Screening recommendations for average-risk patients No upper age limit has been suggested, and the previous recommendation for a "baseline" mammogram between the ages of 35 and 40 has been withdrawn. Thus, both the ACS and the NCCN recommend annual mammography starting at age 40 for women at average risk of breast cancer.

Screening recommendations for high-risk patients Based on epidemiologic evidence that premenopausal familial breast cancer often presents at similar ages among affected family members, many breast imaging centers recommend that yearly screening for such high-risk individuals begin 5-10 years prior to the youngest age at which a first-degree relative was diagnosed with breast cancer. For example, according to this algorithm, a woman whose mother developed breast cancer at age 45 could begin yearly screening at age 35, in addition to biannual clinical

breast examinations. Screening for women at genetic risk may begin at age 25. These commonly used screening algorithms are not based on formal studies but have arisen based on the natural history of the disease. They are, however, in keeping with the recommendations from the NCCN guidelines.

Digital mammography was approved by the US Food and Drug Administration (FDA) in 2000 and is rapidly being adopted by leading breast cancer centers worldwide. Initial trials indicate a comparable sensitivity to film-based mammography, with the benefit of a reduced risk of women called back from screening for additional work-up. The FDA also approved computer-aided detection systems for mammography beginning in 2001. For a small additional fee, mammograms are scanned by a computer and possible lesions are marked for further review by a radiologist. A number of studies have shown a reduced risk of "missed cancers" when computer-aided diagnosis is thus employed.

Two major studies recently demonstrated the increased sensitivity of MRI for detecting breast cancers in women with inherited susceptibility to breast cancer. Kriege et al screened 1,909 women at increased risk and reported the sensitivity of clinical breast examination (CBE), mammography, and MRI was 17.9%, 33.3%, and 79.5%, respectively (20 of 51 tumors were only detectable on MRI). Warner et al screened 236 *BRCA* carriers with CBE, mammography, ultrasonography, and MRI, reporting respective sensitivities of 9%, 36%, 33%, and 77%. The combined sensitivity of MRI plus mammography was 95%, suggesting it may be a viable strategy for screening young women at high-risk for breast cancer (*Kriege M, Biekelmans CTM, Boetes C, et al: N Engl J Med 351:427-437, 2004;Warner E, Plewes DB, Hill KA: JAMA 292:1317-1325, 2004*).

Screening ultrasonography Sensitivity of mammography is diminished when the breast tissue is dense. There have been recent reports in the literature concerning the role of screening breast ultrasonography in women with dense breasts on mammography and normal mammography and clinical breast examination. The results from a multicenter trial of leading breast imagers (ACRIN) may soon become available. Currently, there is no support in the literature for screening ultrasonography, with only anecdotal evidence of adequate sensitivity and specificity. Furthermore, ultrasonography and MRI are used as adjunct studies and should not replace mammography. However, breast MRI appears to be an effective screening tool for high-risk women, particularly those with *BRCA1* and *BRCA2* mutations.

Evaluation of a cystic mass

Fine-needle aspiration When a dominant breast mass is present and the history and physical examination suggest that it is a cyst, the mass can simply be aspirated with a fine needle. Aspiration of a simple benign breast cyst should yield nonbloody fluid and result in complete resolution of the lesion.

Ultrasonography can also be used to determine whether a lesion is solid or cystic and whether a cyst is simple or complex. A complex cyst does not meet the strict criteria of a simple cyst. For example, a complex cyst may demonstrate low level echoes within the cyst fluid or a thickened cyst wall. These features may also

be caused by cyst aspiration (presumably due to postaspiration bleeding); for this reason, many clinicians perform ultrasonography prior to or at the time of FNA.

Biopsy A biopsy is indicated if the cyst fluid is bloody, the lesion does not resolve completely after aspiration, or the cyst recurs after repeated aspirations. Cytologic examination of the fluid is not routinely indicated, as the yield for positive cytology is so low. Cystic carcinoma accounts for < 1% of all breast cancers. However, an intraluminal solid mass is a worrisome sign suggesting (intra) cystic carcinoma and should be biopsied.

Evaluation of a solid mass

A solid, palpable mass can be evaluated in a variety of ways. The decision to observe a patient with a solid breast mass that appears to be benign should be made only after careful clinical and radiologic examinations. Either FNA for cytology or percutaneous core biopsy should also be performed.

Mammography is used to assess the radiologic characteristics of the mass and is important for the evaluation of the remainder of the ipsilateral breast as well as the contralateral breast.

FNA is a simple, easy-to-perform method for obtaining material for cytologic examination. The overall incidence of false-positive results ranges from 0%-2.5% (0.7% when performed by experienced technicians), and the incidence of false-negative results varies from 3%-27% (3%-9% in experienced hands). Reasons for false-negative readings include less-than-optimal technique in preparing the cytologic material, missing the lesion on aspiration, tumor necrosis, and incorrect cytologic interpretation.

Biopsy In the past, an excisional biopsy of a small breast mass or incisional biopsy of a larger breast mass was performed to establish a histologic diagnosis of breast cancer. In recent years, excisional biopsy is being performed less often, except for a presumably benign lesion. For a suspected malignancy, core biopsy is the preferred diagnostic tool. With a core biopsy, the surgeon can plan for the cancer surgery, allowing for definitive surgical management in a single procedure. Core biopsy is also more advantageous than an FNA because architectural as well as cellular characteristics can be evaluated.

Ultrasonography-guided core biopsies

When a palpable mass is extremely deep within the breast or a mass is relatively small, an ultrasonography-guided core biopsy can be performed to increase the diganostic yield. When the procedure is performed with a large core needle (8 to 11 gauge) and vaccum assistance, a mass up to approximately 2-3 cm can be excised.

Ductal lavage

Ductal lavage is currently being developed and analyzed as a minimally invasive tool to identify cellular atypia within breast ducts in women who are already at high risk for developing breast cancer. Nipple aspiration is performed and those ducts that produce fluid undergo lavage. The ductal orifice is cannu-

lated and infused with 2-6 mL of saline. The ductal effluent is collected and evaluated by cytology. A careful record is maintained of each duct that has been lavaged by means of a nipple grid and photography.

The results of the cytologic evaluation may then be used to guide women in their decision-making process with respect to interventions to reduce their risk for breast cancer. Those high-risk women who undergo ductal lavage and the cytology is benign could undergo repeat lavage in 1-3 years. The optimal time for repeat lavage is not currently known. When mild atypia is identified by ductal lavage, the location of the duct should be carefully recorded using a nipple grid and photography to ensure the accurate localization of the duct. A repeat lavage can then be performed in 6-12 months. Women who have benign cytology and mild atypia on ductal lavage should also consider tamoxifen or participation in a chemoprevention trial.

Severe atypia is seen in approximately 6% of women who undergo ductal lavage. Patients with severe atypia on ductal lavage should undergo a thorough evaluation, including a repeat lavage, to confirm this diagnosis and exclude malignancy. The evaluation could also include repeated mammography with ductography, breast MRI, and/or ductoscopy. If no suspicious lesions are found, patients should be carefully followed. Fewer than 1% of patients have had malignant cells identified on ductal lavage.

The lavage of the duct producing the malignant cells should be repeated to confirm the diagnosis. If the diagnosis is confirmed, patients should then undergo the same evaluation as patients with marked atypia. Any suspicious lesion should be biopsied. Patients without suspicious lesions can be offered duct excision after the ductal system has been injected with dye or after close follow-up. These patients should also consider tamoxifen.

Evaluation of nonpalpable mammographic abnormalities

Excisional biopsy Prior to 1991, almost all nonpalpable mammographic lesions were excised using surgical excision. This technique has become less prevalent with the availability of image-guided percutaneous biopsy techniques.

Stereotactic and ultrasonography-guided core biopsies have revolutionized the management of nonpalpable breast lesions, and currently the majority of biopsies can be performed percutaneously, which is quicker, less invasive, and less expensive than excisional biopsy. Tissue acquisition is performed with automated core needles or directional vacuum-assisted biopsy probes. Guidance for percutaneous biopsy is usually provided by stereotaxis, ultrasonography, and, more recently, MRI.

Numerous studies comparing the sensitivity and specificity of stereotactic biopsy vs surgical biopsy have consistently found the two procedures to be statistically equivalent. The long-term false-negative rate for stereotactic biopsy is 1.4%, which equals best published results with surgical biopsy.

Up to 80% of patients with nonpalpable mammographic lesions are candidates for stereotactic core biopsy. Lesions near the chest wall or immedi-

TABLE 5: Examples of eligible risk profiles used in the Breast Cancer Prevention Trial

Age (yr)	Risk profile
35	Two affected first-degree relatives plus personal history of biopsy
40	Two affected first-degree relatives plus no live births
45	Two affected first-degree relatives *or*
	One affected first-degree relative plus personal history of biopsy

ately behind the nipple often cannot be reached on the stereotactic table. Diffuse lesions, such as scattered calcifications or a large asymmetric density, are subject to undersampling with the percutaneous approaches. Some patients are unable to lie prone on the stereotactic table for the duration of the examination. Finally, stereotactic units and trained personnel are not universally available.

Ultrasonography-guided core biopsies are another accurate percutaneous technique, useful for lesions best imaged by ultrasonography. Since the biopsy gun is handheld and guided in real time by the ultrasound imager, there is more variability in performance, depending on the experience and skill of the practitioner. The overall reported accuracy rate of ultrasonography-guided biopsy is comparable to rates achieved with stereotactic and surgical biopsies.

Ultrasonography-guided or stereotactic FNA is another biopsy option. Although somewhat less invasive than core biopsy, FNA provides only cytologic (not histologic) pathology results. This technique can result in both false-positive and false-negative results, whereas a false-positive result has not been reported to date for core breast biopsies. FNA is most successful in centers that have an experienced cytopathologist, who, ideally, is available on site to review smears for adequacy during FNA procedures.

Breast MRI is a sensitive tool for detecting occult breast cancer foci. Due to its limited specificity, high cost, and recent study findings, however, MRI is not likely to become a screening tool for average-risk women. A recent study indicated that breast MRI was superior to mammography and/or ultrasonography for detecting breast cancers in high-risk women (ie, *BRCA* gene mutation carriers).

MRI is currently used primarily to search for a subtle primary breast carcinoma in a patient with metastatic disease, to evaluate the extent of disease in a biopsy-proven breast carcinoma (useful if breast conservation is being considered), or to screen high-risk women with dense breasts on mammograms and nondiagnostic ultrasonography. There is increasing availability of imaging centers capable of MRI localization of breast lesions. The interpretation of breast MRI exams has recently been facilitated by the development of CAD (computer-aided detection) software.

Ultrasonography Stavros et al have described ultrasonographic features of solid masses that suggest benign or malignant disease, such as sharp margins (benign) and taller-than-wide lesions (malignant). Although these features are useful for clinical decision-making, their utility in increasing the specificity of the breast lesion work-up has not been verified.

Sestamibi nuclear medicine scanning can help differentiate benign from malignant mammographic asymmetries and may play a role in evaluating palpable masses. Due to its limited spatial resolution and scatter, this technique is not reliable for lesions 1 cm or smaller.

The Continuing Outcomes Relevant to Evista (CORE) trial, a 4-year follow-up to the Multiple Outcomes of Raloxifene (MORE) trial that examined the effect of long-term therapy with raloxifene (Evista) in postmenopausal women with breast cancer, found that daily intake of the agent reduced the risk of invasive breast cancer by 59%. Compared with placebo, the incidence of invasive estrogen-receptor–positive breast cancer was also reduced in the raloxifene arm ($P < .001$). Women who took raloxifene were more likely to develop blood clots in their legs or lungs, but the increased risk was not statistically significant. However, long-term use of raloxifene did not increase the risk of uterine cancer, as does long-term use of tamoxifen (*Martino S, Cauley JA, Barrett-Connor E, et al: Proc Am Soc Clin Oncol [abstract] 23:97, 2004*).

Prevention

LIFESTYLE CHANGES ASSOCIATED WITH BREAST CANCER RISK REDUCTION

There is increasing evidence that lifestyle changes may alter an individual's breast cancer risk.

Physical activity has been associated with a reduction in breast cancer risk. The benefit was greatest in premenopausal, younger women. The activity can be related to leisure or work-time activities.

It has been suggested that women who exercise 3.5-4.0 times per week have a reduced incidence of breast cancer, compared with women who do not exercise. Exercise's protective effect may be associated with a reduction in the frequency of ovulatory cycles and circulating estrogen and progesterone levels.

Alcohol consumption Numerous studies on the effects of alcohol consumption on breast cancer risk and the results of a cohort study addressing this issue have been published. When compared with nondrinkers, women who consumed 2.3-4.5 bottles of beer per day, 2.5-5.6 glasses of wine per day, or 2-4 shots of liquor per day had a 41% higher risk of developing invasive breast cancer. Some reports indicate that the consumption of a moderate amount of alcohol (red wine) may decrease the risk of breast cancer, although these results are not conclusive. The biologic basis for the association between alcohol consumption and an increased risk of breast cancer is unclear. It has been proposed that there is a positive correlation between alcohol and estrogen levels.

Alterations in diet and tobacco use A reduced incidence of breast cancer has been observed in countries where the diet is typically low in fat. However, no reduction in breast cancer risk has been observed in the United States when

TABLE 6: Number of events among Breast Cancer Prevention Trial participants

Type of event	Placebo	Tamoxifen	Total
Invasive breast cancer	154 (5)[a]	85 (3)[a]	239 (8)[a]
Noninvasive breast cancer	59	31	90
Hip fracture	20	9	29
Colles' fracture	12	7	19
Spinal fracture	39	31	70
Endometrial cancer	14	33	47
All other invasive cancers	88	85	173
Fatal stroke	3	4	7
Nonfatal stroke	21	30	51
Transient ischemic attack	21	18	39
Fatal pulmonary embolism	0	2	2
Nonfatal pulmonary embolism	6	15	21
Deep vein thrombosis requiring hospitalization	3	3	6
Deep vein thrombosis not requiring hospitalization	16	27	43
Total	**456**	**380**	**836**

[a] Numbers in parentheses indicate the number of deaths due to breast cancer.

women followed low-fat diets. An association between red meat consumption or tobacco use and breast cancer risk has not been demonstrated.

Lactation Although it has been suggested that lactation may protect against breast cancer, it is unclear whether lactation reduces breast cancer risk. A recent study failed to demonstrate any breast cancer risk reduction in women who breast-fed and showed no dose-response effect in women who breast-fed for longer periods.

CHEMOPREVENTION

Breast Cancer Prevention Trial

The NIH and NCI have publicized the results of the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT). Women who had a risk of developing breast cancer equivalent to that of women 60 years of age qualified as participants in this double-blind, randomized trial. (For representative eligibility profiles, see Table 5.) A total of 13,388 women were randomized to receive tamoxifen or placebo.

Benefits of therapy The summary results indicate that tamoxifen prevented about half of both invasive and noninvasive breast cancers in all age groups. In addition to this reduction in invasive and noninvasive breast cancer, a secondary benefit of tamoxifen appeared to be a reduction in the incidence of hip fracture (Table 6). At present, no survival advantage has been shown for participants in this trial.

Side effects Tamoxifen-treated women younger than age 50 had no apparent increase in side effects. However, women older than age 50 experienced serious side effects, including vascular events and endometrial cancer. Particularly worrisome was the increased incidence of endometrial cancer in the tamoxifen-treated patients (Table 6). In addition, a significant increase in pulmonary embolism and deep vein thrombosis was noted, especially in women older than age 50 (Table 6).

Current recommendations

Based on results of the BCPT, the FDA has approved tamoxifen for use in women at high risk of breast cancer.

The NCI and NSABP are in the process of developing risk profiles based on age, number of affected first-degree relatives with breast cancer, number of prior breast biopsies, presence or absence of atypical hyperplasia or LCIS, age at menarche, and age at first live birth. These risk profiles may help guide women in making the decision as to whether or not to take tamoxifen.

An ASCO working group published an assessment of tamoxifen use in the setting of breast cancer risk reduction. All women older than 35 years of age with a Gail model risk of > 1.66% (or the risk equivalent to that of women 60 years of age) should be considered candidates for this treatment strategy. Comorbid conditions, such as a history of deep vein thrombosis, must be a part of the consent process and treatment decision.

Although the BCPT results establishing tamoxifen as the standard of care for the primary chemoprevention of breast cancer in high-risk women, concern over the side effects of tamoxifen has prompted a continuing search for an agent that displays a more desirable efficacy/toxicity profile. Raloxifene (Evista), approved for the prevention of osteoporosis in postmenopausal women, displays antiestrogenic properties in the breast and endometrium and estrogenic effects in the bone, making it an attractive candidate for comparison with tamoxifen.

The Study of Tamoxifen and Raloxifene (STAR or NSABP P-2) began in July 1999 at almost 400 centers in North America. A total of19,747 postmenopausal women, or women ≥ 35 years old at increased risk of breast cancer by Gail criteria, were randomized to receive either tamoxifen (20 mg/d) or raloxifene (60 mg/d) for 5 years. Study end points included invasive and noninvasive breast cancer, cardiovascular disease, endometrial cancer, bone fractures, and vascular events. This trial completed accrual in November 2004, and results should be forthcoming.

TABLE 7: TNM staging system for breast cancer

Primary tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	(DCIS) Carcinoma in situ
Tis	(LCIS) Carcinoma in situ
Tis	Paget's disease of the nipple with no tumor
T1	Tumor ≤ 2 cm in greatest dimension
T1mic	Microinvasion ≤ 0.1 cm in greatest dimension
T1a	Tumor > 0.1 but not > 0.5 cm in greatest dimension
T1b	Tumor > 0.5 cm but not >1 cm in greatest dimension
T1c	Tumor > 1 cm but not > 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size, with direct extension to (a) the chest wall or (b) skin only, as described below
T4a	Extension to the chest wall, not including the pectoralis muscle
T4b	Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

Regional lymph nodes (N)

Nx	Regional lymph nodes cannot be assessed (eg, previously removed)
N0	No regional lymph node metastasis
N1	Metastasis in movable ipsilateral axillary lymph node(s); pathologic involvement of one to three axillary lymph nodes
N2	Metastasis in ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent[a] ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis; pathologic involvement of four to nine axillary lymph nodes
N2a	Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastasis only in clinically apparent[a] ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis

Staging and prognosis

Staging system The most widely used system to stage breast cancer is the American Joint Committee on Cancer (AJCC) classification, which is based on tumor size, the status of regional lymph nodes, and the presence of distant metastasis (Table 7).

Clinical staging is performed initially and is determined after the physical examination and appropriate radiologic studies have been performed.

Regional lymph nodes (N) ***(continued)***

N3	Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent[a] ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement; pathologic involvement of 10 or more axillary lymph nodes
N3a	Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
N3b	Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastasis in ipsilateral supraclavicular lymph node(s)

Distant metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage grouping

Stage 0	Tis	N0	M0
Stage I	T1[b]	N0	M0
Stage IIA	T0	N1	M0
	T1[b]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[b]	N2	M0
	T2	N2	M0
	T3	N1-2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ

[a] Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

[b] T1 includes T1mic

From: Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York,

Pathologic staging Pathologic stage is determined following surgery for operable breast cancer. Pathologic tumor size may differ from clinical tumor size. In addition, axillary nodal metastases that were not clinically evident may be detected after pathologic examination.

Prognostic factors Numerous prognostic factors for breast cancer have been identified.

Lymph node status Axillary nodal metastases are the most important prognostic factor. Axillary nodal involvement and survival were evaluated in patients with breast cancer. Survival was examined relative to the number of nodes involved and the location of nodes that contained metastatic deposits. For any given number of positive nodes, survival was independent of the *level* of involvement but was directly related to the *number* of involved nodes.

Overall, patients who have node-negative disease have a 10-year survival rate of 70% and a 5-year recurrence rate of 19%. As the number of positive nodes increases, so does the likelihood of relapse. Patients with > 10 positive lymph nodes have a recurrence rate of 72%-82%. The majority of patients who develop recurrence after initial curative treatment for early-stage breast cancer will have distant metastases.

Hormone-receptor status In general, hormone receptor-positive tumors have a more indolent course than do hormone receptor-negative tumors. However, the hormone-receptor status of a tumor is a stronger predictive than prognostic factor. That is, hormone receptor-negative tumors are unlikely to respond to endocrine therapy in contrast to hormone receptor-positive tumors.

Other factors that have been utilized to predict outcome are histologic grade, lymphovascular permeation, S-phase fraction, and ploidy.

More recently, molecular prognostic factors have been evaluated to determine their utility in predicting outcome. They include the growth factor receptors (epidermal growth factor receptor and c-*erb*B-2/*neu*), tumor-suppressor genes *(p53)*, proteolytic enzymes that may be associated with invasion of disease and metastasis (cathepsin D), and metastasis-suppressor genes *(nm23)*.

Of these molecular markers, HER-2/*neu* or c-erbB-1/*neu* is probably the most widely studied in breast cancer to date. HER-2/*neu* amplification is often associated with a more aggressive behavior and thus poorer outcome for patients with HER-2/*neu*-positive tumors. Fortunately, targeted therapy with trastuzumab (Herceptin) has changed the course for treatment, providing longer survival when used in combination with chemotherapy for patients with metastatic disease.

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